Gender Medicine in Gastroenterology

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ABSTRACT: The cause for gender differences in the epidemiology, natural history and response to therapy in many diseases is unknown and has seldom been investigated in depth. Sex hormones are blamed for many of these changes, mostly without any scientific evidence. In this review I will describe some of the evidence for gender differences in gastrointestinal diseases. Gender medicine and its application for gastroenterology is a new field and one warranting research.

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The effect of gender on gastrointestinal diseases is well known, and although recognized for decades the subject has hardly been investigated. Some diseases are dominated by the female gender, such as gallstone disease or primary biliary cirrhosis [1,2], and some by the male gender, for example, gastroesophageal reflux disease or primary sclerosing cholangitis [3,4]. The cause of these observed gender differences is unknown and has seldom been studied in depth. Sex hormones are frequently blamed for gender-dependent changes in disease prevalence, mostly without any scientific evidence. Gender differences may be found not only in the epidemiology of diseases, but also in their natural history and response to therapy.

EPIDEMIOLOGY

In a retrospective analysis of 466,855 adolescents aged 16 for the period 1998 to 2003, we found significant differences between genders in the prevalence and incidence of peptic ulcer disease, irritable bowel syndrome, lactose intolerance, celiac disease and gallbladder disease – all with a female predominance [5]. These findings were particularly marked for peptic ulcer and gallstone diseases ($P < 0.001$ for both). A trend for female predominance in irritable bowel syndrome and peptic ulcer disease was confirmed in another report of a somewhat older population attending a military clinic [6].

The incidence of colonic adenomatous polyps and colorectal cancer is lower in younger women than men

DISEASE OUTCOME

In a retrospective case-control study we evaluated all patients admitted to our medical center due to non-variceal upper gastrointestinal bleeding [7]. We could characterize two types of bleeding – primary (patients admitted because of bleeding) and secondary (when bleeding started in hospital). There were significantly more men in the primary bleeding group and more women in the secondary bleeding group. In a recent study from Korea, Kim and colleagues [8] found that the 10-year survival in patients with gastric cancer was higher in young men and older women. When Crohn's disease is considered, more cases of lower abdominal pain were described in women and a differential diagnosis with ovarian cyst, endometriosis and pelvic inflammatory disease should be considered. In addition, other factors need to be considered, such as recurrent symptoms synchronized with the menstrual cycle, increased risk from use of contraceptives, abnormal Pap smear, and the use of immune modulators, as well as the risk of biologic agents crossing the placenta [9-11].

RESPONSE TO THERAPY

Recently, we demonstrated a different response of women, compared to men, to the eradication of *Helicobacter pylori* by means of a proton pump inhibitor, antibiotics and cranberry juice. The difference was suspected to be due to the different concentration of the bacteria in men compared to women [12]. We confirmed this finding by evaluating ^{13}C-urea breath test result in 11,146 patients [13]. We found that the numeric result of the test was significantly higher in women, possibly representing a higher bacterial load.

GENDER AND COLORECTAL CANCER

Almost a million cases of colorectal cancer are diagnosed every year around the world, and almost half a million people die of this devastating disease every year. According to the CORI database, an American endoscopy database of 75 American medical centers, men have a higher risk of polyps (with odds ratio of 1.5) and tumors (OR 1.4) than women [14]. Interestingly,

OR = odds ratio

women have a greater risk of developing pure right-sided polyps (OR 1.2) and tumors (OR 1.6) than men. In the California registry of 52,882 patients with metastatic colorectal cancer, younger women lived longer than men, 17 months on average as compared to 14 months, but older women lived less long than men. These results were highly significant.

Estrogen receptor-β is probably a tumor suppressor gene in colorectal cancer, directs neoplastic cells toward apoptosis and prevents proliferation

We evaluated prospective colonoscopy studies for screening CRC and early detection of polyps in the average-risk asymptomatic population [15]. The maximal detection rates of adenomas, advanced adenomatous polyps and CRC were higher in men than in women. The detection rate for adenoma was 35.7% vs. 15.5%, for advanced adenomatous polyp it was 10.3% vs. 4.8%, and for CRC 1% vs. 0.48%. Similarly, gender differences in the incidence of CRC were evaluated in inflammatory bowel disease patients [16]. A population base of 7607 IBD patients was followed for 44 years in Sweden, totaling 171,000 person-years of follow-up. The authors found 196 new cases of CRC, 123 in men and 73 in women. Men had a 60% higher risk, 8.3% vs. 3.5%. Again, this observation held only for patients under the age of 45. Thus, the incidence of adenomatous polyps, advanced adenomatous polyps and colorectal cancer was lower in younger women than men in cases of sporadic CRC and in CRC occurring in longstanding IBD; and survival in patients with metastatic CRC was better in younger women than men [17]. These differences disappeared after age 45, suggesting that estrogen may be protective. Then it was found that hormone replacement therapy protected against CRC and decreased the incidence in 66% of patients after 15 years of therapy [18]. There are two types of estrogen receptors, ERα and ERβ. ERα is a nuclear receptor for 17β-estradiol, on chromosome 6q25, and is present in the female reproductive system. ERβ, on chromosome 14q23, is found in the colon. It was demonstrated that silencing of ERβ by mutation or methylation of the gene promoter increased proliferation and carcinogenesis [19]. ERβ is abundantly expressed in normal colonic mucosa but declines in CRC, paralleling the tumor's dedifferentiation [20]. Loss of ERβ expression in CRC is associated with more advanced staging [21]. Loss of ERβ in knockout mice led to colonic mucosa hyperproliferation and disordered apoptosis [22]. Activation of ERβ induced apoptosis in COLO205 and LoVo CRC cell lines [23,24]. Taking all these data together I assume that ERβ is a tumor suppressor gene in CRC, directs neoplastic cells toward apoptosis and prevents proliferation.

Paradoxically, we demonstrated a higher rate of refusal to participate in a screening project among men, which resulted in a higher incidence and mortality rate from CRC [25]. Annual screening with fecal occult blood test was offered to 3548 average-risk individuals; 1010 refused, 2538 agreed, and 1376 were never offered the screening and served as controls. We followed the groups for 7 years. The refusers were more likely to be men and had a higher incidence of CRC than screenees and controls. In another study on screening for CRC, we confirmed the higher participation rate of women [26]. The study comprised 12,539 patients, of whom 7070 (56.4%) were women, in two arms – screening with guaiac fecal occult blood test or with the fecal immunochemical test. We found that female gender (OR 1.29, $P < 0.001$) was associated with higher test compliance. Among women, regression analysis demonstrated that performing mammography (OR 4.55, $P < 0.001$) was associated with compliance.

Gender medicine, and its application for gastroenterology, is a new field that warrants research

CONCLUSION

Gender differences are clearly an important factor in the epidemiology, clinical presentation, management and outcome of gastrointestinal diseases. Gender medicine, and its application for gastroenterology, is a new field that warrants research.

CRC = colorectal cancer
IBD = inflammatory bowel disease
ER = estrogen receptor

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